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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,049	06/22/2001	Yasuki Kato	506.40278X00	1134

7590 07/01/2003

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EXAMINER
SRIVASTAVA, KAILASH C

ART UNIT	PAPER NUMBER
1651	14

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/869,049	YASUKI KATO ET AL.	
	Examiner	Art Unit	
	Kailash C. Srivastava	1651	

-- Th MAILING DATE f this communication appears on the c ver sheet with the correspondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5&9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Request for continued examination (i.e., RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 10, 2003 as Paper Number 12 has been entered. Accordingly an RCE has been established and the action on RCE follows.

2. Applicants' response and Amendment filed April 10, 2003 as Paper Number 12 in response to Office Action mailed October 10, 2002 as paper number 10 is acknowledged and entered.

3. Claims 1-30 are pending.

4. Claims 1, 2,5, 7, 9,13, 17, 21, 23 and 27 have been amended.

5. Claims 1-30 are examined on merits.

Information Disclosure Statement

6. Applicants' revised Information Disclosure (i.e., IDS) originally filed August 15, 2001, 2002 as Paper Number 5 and copy of the PTO form 1449 originally submitted on June 3, 2002 as paper number 9 along with the copies of all the WO documents listed in the latter form 1449 are acknowledged. With this submission applicants have overcome the objection to IDS in Office Action mailed October 10, 2002 as paper number 10. The two IDS documents cited supra have been made of record and considered.

Claim Rejections - 35 U.S.C. § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

8. Claims 1-30 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not present any support to show how applicants have determined presence or absence of an amide bond in the product (i.e., "that can be obtained") resulting from reaction between a compound comprising a free amino group and a reducing sugar because only method of analyses that the applicants have recite are the HPLC to identify the product formed (Examples 1 and 2) and an enzymatic method to assay insulin (Examples?) in the blood. Applicants have also not disclosed the identity of the resulting compound recited in Tables 1 and 2.

9. Claims 1-30 are rejected under 35 U.S.C.§ 112, first paragraph, because the specification, while being enabling for peptides, proteins, enzymes and amino acid derivatives, does not reasonably provide enablement for all the compounds having a free amino group. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. While the specification specifically enables bovine pancreatic insulin, Enkephalin, doxorubicin hydrochloride and other peptides, to claim all compounds having a free amino group or even to all insulin is to claim too broad coverage for applicants' invention. Similarly, applicants' claimed invention is exemplified with only two "sugars having the reducing power" (i.e., β–lactose and sialyllactose, and despite a long list of sugars with reducing power (Specification Page), applicants' preferred sugars with reducing power are: disialyllactose, galactose, lactose and sialyllactose, See specification, Page 5, Lines 29-30) but not to all "sugars having reducing power".

An artisan in the art would not be able to practice the invention because an undue experimentation will be required to obtain the compounds cited *supra*. Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary to determine a method that would show the presence or absence of a new amide bond; limited amount of guidance and limited number of working examples in the specification because none of the examples recite a method to determine the type of bond or whether the invention would be applicable to peptides other than bovine pancreatic insulin; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

10. Applicants' arguments regarding the rejections to Claims 1-30 under 35 U.S.C.§ 112, first paragraph in the Office Action mailed October 10, 2002 as paper number 10 have

been fully considered but are not deemed persuasive. Applicants argue that the specification is fully enabled for any compound having a free amino group because the specification recites no restrictions for the compound with free amino group. Applicants further argue that they have conducted experiments with two distinct compounds and in each case the results indicate that their inventive concept is applicable. However, based upon the teachings provided by the instant specification, the specification is still deemed enabled for only insulin, Enkephalin, doxorubicin hydrochloride and peptides, but not for all other compounds that contain free amino group for the reasons of record discussed in previous Office actions (i.e., those mailed on 09/14/2001 as paper number 3 and on October 10, 2002 as paper number 10).

11. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> ***The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.***

12. Claims 1-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1 as written is very confusing, difficult to understand and thus indefinite. From the current recitation, Claim 1 does not clarify as to what is being released, the compound with free amino group, the sugar having the reducing power, or the product of the reaction between the compound with free amino group and the sugar having the reducing power? Applicants are requested to clearly, concisely and succinctly rewrite said claim in such a manner that the claims clearly indicate the applicants' invention. Applicants are reminded to ensure that no new matter I added while rewriting said claim.

- The phrase, "which can be obtained" in Claims 1, 5, 9, 13, 17, 23, and 27 renders those Claims indefinite because it is unclear as to how the disclosed/claimed compound will be prepared by "reacting a compound having free amino group with a sugar having the reducing power". Applicants should delineate each and every step in the claim language because a method is being disclosed/claimed. Furthermore, the phrase, "can be obtained" gives the connotation of a future occurrence without affirmative claiming the disclosed/claimed process.

- The recitation, "derivative" in claims 1-2, 5,7, 13 and 21 renders those claims unclear and confusing, and therefore indefinite because the term does not clearly define as to how similar a compound should be of the base compound to be called derivative, i.e. the term does not define the metes and bounds of the claimed subject matter.

- The recitation, "capable of" in claim 1 renders that claim unclear and confusing, and therefore indefinite because the term does not define the metes and bounds of the claimed subject matter.

- The phrase "modified with or included in" renders Claims 5, 9, 13, 17, and 23 confusing. Applicants should clarify whether this term is open, like the conventional term "comprising", or what does this term define? The Examiner suggests that the applicants should replace this phrase with the transitional phrase "further comprising".

- Claims 7-8, 11-12, 15-16, 19-20, 25-26 and 29-30 are rendered indefinite because of the term "including". This term is similar to term "include" and is therefore, indefinite because it is not clear whether the term is open, like the conventional term "comprising" or whether the term excludes other ingredients, like the term "consisting of". It is suggested that the applicants use the transitional phrase -"comprises".

All other claims depend directly from the rejected claims cited *supra* and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

13. Applicants' arguments regarding the rejections to Claims 1-30 under 35 U.S.C.§ 112, second paragraph in the Office Action mailed October 10, 2002 as paper number 10 have been fully considered but are not deemed persuasive. Applicants argue that the phrase, "modified with or included in" is described in the specification and the meaning of the said phrase would be clear to those skilled in the art. However, phrase "modified with or included in" is still indefinite for the reasons of record discussed in previous Office actions (i.e., those mailed on 09/14/2001 as paper number 3 and on October 10, 2002 as paper number 10) and as discussed above.

Claim Rejections – 35 U.S.C. § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

15. Claim 1 is rejected under 35 U.S.C. §102(b) as anticipated by Sessler et al. (U.S. Patent 5,580,543).

Claim recites a composition comprising a compound formed via interaction of a compound with free amino acid group, wherein said free amino group containing compound is a peptide, with a sugar having reducing power, wherein a new amide bond is not formed and said product rapidly releases the compound with free amino groups in response to pH changes.

Sessler et al. teach a pharmaceutical composition comprised of a peptide and a saccharide, wherein said peptide is a hormone or enkephalin and said saccharide anyone of D-glucose, D-mannose or D-galactose (Column 7, Lines 14-30; Column 8, Lines 22-25; Column 10, Lines 55-57 and Column 11, Lines 49-54). Said composition is formed without any amide bonds (Column 25, Lines 63-64) and said peptide binds to a receptor under appropriate conditions of pH, ionic strength etc. (Column 7, Lines 14-30). Thus, the prior art teaches a composition, comprising same ingredients, wherein, said composition, upon being subjected to changes in pH behaves in the same manner as the claimed invention. Therefore, the prior art reference is inherently teaching the same composition as claimed because a composition comprised of same ingredients, behaving in same manner as the compound in claimed invention is disclosed in the prior art reference.

Therefore, the reference deems to anticipate the cited claim.

16. Applicant's arguments with respect to claims 1-4 filed on April 10, 2003 as Paper Number 12 in response to Office Action mailed October 10, 2002 as paper number 10 in regard to rejections to claims 1-4 under 35 U.S.C. § 102(b) have been considered but are moot in view of the applicants' amendment and new ground(s) of rejection discussed *supra*.

Claim Rejections - 35 U.S.C. § 103

17. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § *102*(f) or (g) prior arts under 35 US.C. § 103(a).

19. Claims 1-30 are rejected under 35 U.S.C. § 103 (a) as obvious over Sessler et al. (U.S. Patent 5,580,543) in view of Katsukiyo (JP-07-061999) and Masashi et al (JP 9-263579).

Claims recite a pharmaceutical composition comprising a compound obtained through reacting a compound having a free amino group with a sugar having the reducing power, wherein the resultant compound is modified with or embedded in a pharmaceutical carrier and upon changes in pH conditions, said compound with free amino group is released. Said compound with free amino group is insulin or another peptide. Said pharmaceutical carrier may be anyone among: liposome, lipid emulsion, microemulsion, polymer micelle, microcapsule, microspheres and magnetic particles.

Teachings from Sessler et al. have already been discussed *supra*.

Sessler et al., however, do not disclose insulin to be the peptide with free amino group. They also do not clearly disclose a pharmaceutical carrier (e.g., liposome, lipid emulsion, microemulsion, polymer micelle, microcapsule, microsphere or magnetic particles).

Katsukiyo discloses a sugar-modified protein wherein lactose lactone is reacted with a protein, the said protein being insulin, to make a protein reducing sugar complex (Paragraph 17, Lines 1-6). Since Katsukiyo et al disclose a similar product prepared in the manner instantly disclosed, the product would intrinsically function in the same, or essentially the same manner as in the claimed invention. Therefore, the product disclosed in the prior at reference would intrinsically free the compound with free amino acid group (i.e.,

insulin) upon changes in the pH.

Katsukiyo, however, does not disclose that the protein-reducing sugar complex product resulting from reacting insulin (i.e., a peptide with a free amino group) with sugar having the reducing power is embedded in a pharmaceutical carrier, wherein said pharmaceutical carrier is an emulsion, microglobule, ribosome or other pharmaceutical carrier.

Masashi et al., teach medications made from enclosing a drug made from protein inserted into a microglobule, ribosome, emulsion or other carrier (e.g., Claims 6 and 12).

An artisan of ordinary skill would be motivated to modify the teachings from Sessler et al. (Column 7, Lines 14-30; Column 8, Lines 22-25; Column 10, Lines 55-57; Column 11, Lines 49-54 and Column 25, Lines 63-64) according to the teachings of Katsukiyo (Paragraph 17, Lines 1-6) and Masashi et al. (e.g., Claims 6 and 12), because both Sessler et al., and Katsukiyo teach modifying a compound with free amino group with a sugar having the reducing power, wherein upon changes in the pH conditions, the compound with free amino group is released from the product resulting from the reaction between said peptide and sugar having the reducing power and Masashi et al., further teach making a drug by inserting a protein into microglobule, ribosome, emulsion or other carrier. Thus, Katsukiyo remedies the deficiency in teachings of Sessler et al. about said peptide being insulin, while Masashi et al., remedy the deficiency in the teachings of both Sessler et al., and Katsukiyo about said pharmaceutical carrier.

Since each one of the cited prior art references teach a composition comprising ingredients that are common to instantly claimed compositions (e.g., a protein/ drug), it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings from each one of the cited references to obtain a pharmaceutical composition comprising a compound with free amino group modified with a sugar having the reducing power and inserting the resultant compound in a pharmaceutical carrier, wherein said free amino group containing compound is released upon changes in pH.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary

skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. Applicant's arguments filed on April 10, 2003 as Paper Number 12 in response to Office Action mailed October 10, 2002 as paper number 10 with regard to rejections to claims 1-30 under 35 U.S.C. § 103(a) have been considered but are moot in view of the applicants' amendment and new ground(s) of rejection discussed *supra*.

CONCLUSION

21. No Claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (703) 605-1196. The examiner can normally be reached on Monday-Thursday from 7:30A.M. to 6:00 P. M. (Eastern Standard or Daylight Saving time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1651
(703) 605-1196

June 30, 2003

LEON B. LANKFORD, JR.
PRIMARY EXAMINER